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A REVIEW ON MONOSODIUM GLUTAMATE

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INTRODUCTION

MSG (MW: 187.13) is typically marketed as a white crystalline powder and is readily soluble in water but sparingly soluble in ethanol. MSG is not hygroscopic and is considered quite stable in that it does not change in appearance or quality during prolonged storage at room temperature. MSG does not decompose during normal food processing or cooking but in acidic conditions (pH 2.2-2.4) and at high temperatures it is partially dehydrated andconverted into 5-pyrrolidone-2-carboxylate[1].

Monosodium L- glutamate (MSG) is the sodium salt of the Glutamic acid[2] (Figure 1). Glutamate is one of the richest amino acids that make up proteins. It is found in protein rich foods such as milk, meat, fish, cheese, tomato products, soy sauces, and in many animal tissues and is responsible for their savoury taste[3]. It is produced commercially by the fermentation of molasses and fermented proteins (soy sauce and hydrolyzed vegetable protein). Glutamate is also produced in the body and plays an important role in humanmetabolism[4]. MSG is used as flavouring agent and its consumption has increased throughout the world in recent years as flavoring in cookingto increase palatability and food selection in a meal[3,5,6]. It is used in foods to provide various taste such as meaty, savoury, or brothy taste by stimulating the glutamate receptors located on the tongue. There are glutamate receptors in other parts of the body also, especially in the brain, where glutamate is acting as a neurotransmitter. These receptors induces more salivation, create greater stimulation of the olfactory and limbic system of the brain and promotes immune function[7].

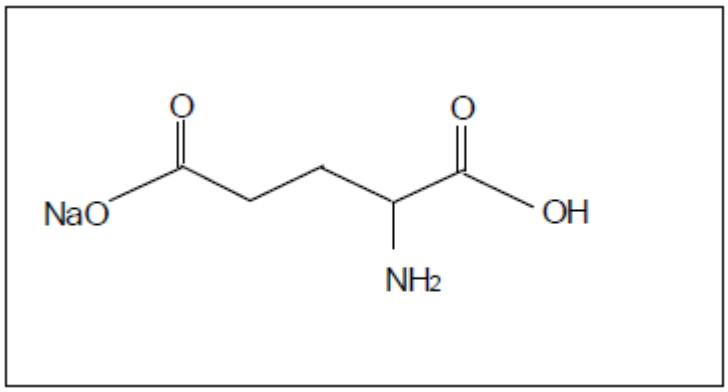

Figure 1: Chemical structure of MSG

Almost all dietary glutamateare available in free form and in protein constituent form. Dietary glutamate is a major energy source and an important substrate for the synthesis of glutathione and other amino acids in the gut. These glutamate are metabolized in intestinal mucosa [8]. The average intake of glutamate as protein constituent (10g) and in its free form has been estimated

approximately 1g/day[9]. With respect to added glutamate mostlyin the form of MSG, the average intake ranges from 0.3 to 0.5 g/day in European countries and 1.2 to 1.7 g/day in Asian countries[9]. These levels of glutamate in the food are considered as safe[9,10].

Table1: Free glutamate in the organs [11]

Tissue	**Free glutamate (mg)**
Muscles	6000
Brain	2250
Kidney	680
Liver	670
Blood plasma	40
Total	9640

In the late 1960s numerous case reports appeared in the scientific literature describing a complex of symptoms which originated to be known as the Chinese restaurant syndrome (CRS) because they typically followed ingestion of a Chinese meal. Investigations have mostly focussed on MSG as the causative agent in CRS. The most frequently reported symptoms of MSG are burning sensation of different parts of the body, headache, chest pain, nausea or vomiting[12], numbness/tingling, flushing, muscle tightness, neuroexcitotoxicity[13,14], obesity[15,16], impaired vision[17], flushing, sweating and generalized weakness[16]. More recently, the term MSG symptom complex has been used instead of CRS.

Numerous mechanisms for CRS have been proposed of which some mechanisms assume an involvement for MSG while others do not.

The proposed mechanisms for CRS resemble an immediate hypersensitivity reaction in which the symptoms occur naturally within a few minutes to some hours subsequently eating the offending food. However, there is no evidence for an IgE-mediated reaction exists, although the possibility of an anaphylactoid reaction cannot be reduced. There are other non-allergenic mechanisms which may give rise to CRS such as acetylcholinosis, vitaminB6 deficiency, reflux oesophagitis, and histamine toxicity[18].

The another proposed mechanisms for CRS involve an increase in acetylcholine produced by the ingestion of MSG in large doses. These ingested glutamate get converted toacetylcholine via the tricarboxylic acid (TCA) cycle. A similarity between the symptoms ofCRS and those happening after injection of acetylcholine (flushing, feeling of warmth,throbbing in the head, palpitations,

and sub-sternal constriction) was noted and it has also beenobserved experimentally that in humans there is a 28% decrease in cholinesterase after MSGis consumed. The symptoms of CRS were also found to be capable of modulation using drugs affecting the cholinergic mechanisms[19].

The proposed mechanisms assume that the reactions experienced by MSG-sensitive individuals are a result of vitamin B6 deficiency. They found that when MSG responders established supplemental B6, CRS symptoms were prevented [20].

The proposed mechanisms assume that the symptoms seen in CRS are caused by MSG but are not by a neurological/physiological reaction. CRS is actually a case of reflux oesophagitis, with MSG acting as an oesophageal irritant [21]. The symptoms and regions of the body affected by CRS were noted to be similar to those of pain referred from the upperesophagus. There are various substances such ascoffee, orange juice and tomato juice, ingested through oesophageal infusion, can cause similar types of symptoms[22].

Chin KW et al,(1989) proposed that there are similarities between CRS and scombroid poisoning, caused by naturally occurring histamine in foods and therefore he assayed some chinese restaurant dishes and condiments for histamine content. It wasconcluded that the histamine content of most of the foods assayed was not sufficientalone to cause histamine toxicity, in certain situations histamine intake over the course of anentire meal could approach toxic levels[23].

Table 2:Naturally occurring glutamate in various food[1].

Food	**Bound glutamate (mg/100g)**	**Free glutamate (mg/100mg)**
Milk/dairy product:		
Cow's milk	819	2
Human milk	229	22
Parmesan cheese	9847	1200
Poultry products:		
Eggs	1583	23
Chicken	3309	44
Duck	3636	69
Meat:		
Beef	2846	33
Pork	2325	23
Fish:		
Cod	2101	9
Mackerel	2382	36
Salamon	2216	20
Vegetables:		
Peas	5583	200
Corn	1765	130
Carrots	218	33
Spinach	289	39
Tomatoes	238	140
Potato	280	180

Table 3: Free glutamate content of traditional seasonings, various packaged food and restaurant meals[24]

Food type	**Free glutamate content (Mg/100mg)**
Concentrated extract	
Vegemite	1431
Marmite	1960
Oyster sauce	900
Soy sauce	
China	926
Japan	782
Korea	1264
Philippines	412
Fish sauce	
Nam-pla	950
Nuoc-mam	950
Ishiru	1383
Bakasang	725
Condensed soups	20-1900
Sauces ,mixer, seasonings	<10-1500
Italin restaurant meals	10-230
Western restaurant meals	<10-710

Glutamate in metabolism

Glutamate performsnumerous essential roles in intermediate metabolism and is present inlarge amounts in the organs and tissues of the body. The daily intake of glutamate in the adult human has been estimated as 4800mg [25]. Some of the important metabolic parts of glutamate include:

1. A substrate for protein synthesis – as one of the most abundant amino acids present in nature, containing between 10 – 40% by weight of most proteins, L-glutamic acid is an essential substrate for protein synthesis. Glutamic acid possesses physical and chemical features which make it a principal giver to the secondary structure of proteins, namely the α-helices [26].

2. A transamination partner with α-ketoglutarate – L-glutamate is synthesized from ammonia and α-ketoglutarate (an intermediate of the citric acid cycle) in a reaction catalyzed by L-glutamate dehydrogenase. This reaction is of major importance in the biosynthesis of all amino acids, since glutamate is the amino group donor in the biosynthesis of other amino acids through transamination reactions [27].
3. A precursor of glutamine – glutamine is formed from glutamate by the action of glutamine synthetase. This is also an important essential reaction in amino acid metabolism since it is the main pathway for converting free ammonia into glutamine for transport in the blood. Glutamate and glutamine are therefore key associations between carbon and nitrogen metabolism in general and between the carbon metabolism of carbohydrate and protein in specific[28.]
4. A substrate for glutathione production – glutathione, a tripeptide composed of glutamic acid, cysteine and glycine, is present in all animal cells and helps as a reductant of toxic peroxides by the action of glutathione peroxidase. Glutathione is also assumed to function in the transport of amino acids across cell membranes [27].
5. A precursor of N-acetylglutamate – an essential allosteric activator of carbamyl phosphate synthetase I, importantcontrolling enzyme in the urea cycle, confirming that the rate of urea synthesis is in accord with rates of amino acid deamination [29].
6. An important neurotransmitter – glutamate is the major excitatory transmitter within the brain, mediating fast synaptic transmission and is active in possibly one third of central nervous system synapses . Glutamate is also a precursor to another neurotransmitter GABA[30].
7. An important energy source for some tissues (mucosa) – intestinal tissues are responsible for significant metabolism of dietary glutamate, where it helps as a significant energy softsubstrate. A remaining effect of the extensive intestinal metabolism of dietary glutamate is a relatively stable plasma glutamate concentration throughout fasting and fed periods[26].

Table 4: Review of effect of monosodium glutamate in various system in mice/rats.

Sr. No.	System	Dose	Duration	Species	Effect observed	Ref.
1.	Central Nervous System	4mg/g, S.C	Postnatal days 1,3,5 and 7.	Rats	Prefrontal cerebral cortex changes, including fewer neurons, shorter and less ramified dendritic processes, loss of cortical cell, 30% and 40% reduction of pituitary weight in ages of 6 and 12 months, Increased proopiomelanocortin mRNA levels and adrenocorticotropic hormone, neuronal cell death with reduction of photoreceptor and glial cells.	27,28,29,30,31, 32,33.
		2.5gm/kg, oral	14days	Rats	Degeneration and loss of corticalneurons particularly the Purkinje cells.	34.
		2 g/kg MSG dissolved in PSS or sodium chloride solution at an equimolar concentration . I.P	7days	Rats	Reduced body weight, locomotor activity, muscle grip strength and foot fault.	35.
		14.0, 42.8 or 42.0gm/kg		Mice	No pathological changes in the hypothalamic arcuate nuclei of pregnant and lactating female rats and their fetuses, sucklings, and weanling mice observe	36.
		3mg/kg	14 days	Rats	Histological examination of cerebellar cortex showed degenerative changes as pyknotic purkinje and granule cells with areas of degeneration surrounded by inflammatory cells in granular layer, activation of both the gastric and the celiac branches of the vagus nerve led to the activation of the insular cortex, limbic system, hypothalamus and nucleus tractus solitaries.	37,38.
		2.5mg/g or 4mg/g1	17-21days of pregnancy	Mice	Impaired Y-maze discrimination learning in the 60 day.	39.
		2mg/g	10 days	Rats	Decrease in the active avoidance learning performance at the 90^{th} post–dosing day.	40.
2.	Effect on Obesity and Metabolic Disturbances	2mg/g and 4mg/g	Postnatal days 2, 4. And postnatal day 6, 8, 10.	Rats	Increased mRNA expression of interleukin-6, tumor necrosis factor alpha, resistin and leptin in visceral adipose tissue, it increased insulin, resistin and leptin levels in serum and it also impaired glucose tolerance.	41.
		0.04mg/kg and 0.08gm/kg	42days	Rats	Degenerative changes on the liver and dilatation of the central vein	42.
		0.6mg/g	10days	Rats	Increased lipid peroxidation, decreased reduced glutathione level and increased activities of glutathione-transferase, catalase and superoxide dismutase.	43.
		2mg/day	6 day	Rats	Increased levels of some circulating amino acids (leucine, isoleucine, valine, lysine, cysteine, alanine, tyrosine, and tryptophan)	44.
3.	Reproductive	2mg/g S.C	Perinatal	Mice	Increase in the number of the pachytene stage of	45.

	System		period 2nd, 4th, 6th, 8th, 10th days		primary spermatocyte at the 75th day.	
		4mg/g	Perinatal period 2nd, 4th, 6th, 8th, 10th days	Newborn male rats	Decreased weight of pituitary glands and testes and lowered testosterone level in 4 months.	46.
		2mg/g S.C	Perinatal period 2nd, 4th, 6th, 8th, 10th days	Female mice	Increased number of the primary Follicles without any increase in number of Graffian follicles in ovarian tissue at the 75th day.	47.
		0.04mg/kg OR 0.08mg/kg	Daily	Female rats	Pathological changes have been observed in ovaries and fallopian tube, cellular hypertrophy of the theca folliculi, destruction of the basement membrane and stroma cells` vacuolations in the ovaries, fallopian tube: separation of the endosalpinx from the myosalpinx, vacuolations and lysed red blood cells appeared in some parts of the stroma cells.	48,49.
4.	Eye	High doses	Daily diet for 6 months	Rats	Retinal nerve layers thinned by up to 75 percent. At the end of the six months, all of the rats vision damage.	50.
		10gm (Ratsfed 10gm of sodium glutamate added to a 100gm daily diet.)	Daily diet for 3 months	Rats	Increase in amount of glutamic acid in vitreous, damage to the retina, and deficits in retinal function	51,52, 53.
5.	Immune system	4mg/g, I.P	6days	Rats	Induced apoptosis and changed level of Bcl-2protein in thymocytes related with oxidative stress, increase in oxidative stress with in the kidneys, liver, brain and thymus.	54.
6.	Hematological Parameters	5.5g/kg and 2.75g/kg	14days and 28days	Rats	Decrease in neutrophil and lymphocyte count, hemoglobin (Hb), Red blood cell (RBC) indicative of anemic conditions.	55.
7.	Kidney	830mg/kg, p.o	28 days	Rats	Increase in the Serum creatinine, BUN levels, increase in the urinary excretion of albumin.	57.
		0.6mg/g and 1.6mg/g	14 days	Rats	Increase in the body weight, relative liver weight, serum urea, serum creatinine	57.
8.	Induced physiological Stress		5days	Mice	Induced hyperlipidemia and hyperglycemia and oxidative stress in the red blood cells, peroxidation of membrane lipids and red blood cells	58,59,60,61,62.
		2mg/g (An useful model of (NAFLD in human)	5days	Mice	Produced severe obesity, urinary glucose, hyperglycemia, hyperinsulinemia, and a decrease in both glucose tolerance and insulin sensitivity.	63,64.
		4mg/g, S.C	5days	Mice	Induced immediate severe obesity, decrease growth (due to impaired production of growth hormone).	65,66,67,68,69.
		2mg/g, S.C	5days	Mice	Induced severe body weight, body length, diabetes mellitus, and liver lesions resembling NAFLD/NASH and several kinds of dysfunction of lipid metabolism .	70,71.

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